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X-Ray Crystallographic Analysis of Phosphono Sugar and a Novel Preparation of Phosphono Sugar Nucleoside Derivatives

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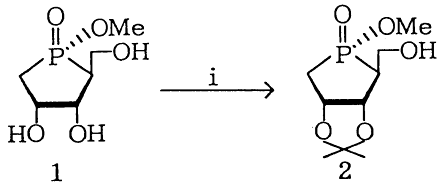
Stereoselective reactions of 1-methoxy-3-phospholene 1-oxide gave a novel 1-deoxy phosphono sugar, whose relative configuration was confirmed by X-ray crystallography. Further reaction of the 1-deoxy phosphono sugar with phthalimide and 6-chloropurine produced novel phosphono sugar nucleosides.

Among a class of hetero sugars, sugar derivatives having a hetero atom in the hemiacetal ring, phosphono sugars are of interest in the aspects related not only to syntheses but also biological activities.[1-4] Nucleosides such as azidothimidine (AZT), which is a useful anti HIV agent with an N_3 substituent on the sugar moiety of the nucleoside,[5] are also biologically important substances. Therefore, preparation of sugar derivatives such as glycosides and nucleosides is an interesting and important field in the carbohydrate chemistry,[6] especially in the field of the hetero sugar chemistry. The synthesis of phosphono sugar nucleosides has not been reported, because the phosphono sugars so far prepared were produced chiefly by many synthetic steps starting from sugar materials,[7] whose transformation into the phosphono sugar nucleosides was actually difficult as yet. We previously reported the stereoselective and short preparation of phosphono sugar from 1-methoxy-3-phospholene 1-oxide.[8] The present communication deals with the synthesis of novel phosphono sugar derivatives and the structural elucidation by X-ray crystallographic analysis, and the novel synthesis of phosphono furanose nucleosides via a phosphono sugar by a nucleophilic substitution and dehydration.

Reaction of 1-deoxy phosphono sugar **1**[8, 9] with acetone in the presence of sulfuric acid and copper(II) sulfate for 2 d at room temperature gave regiospecifically 2,3-*O*-isopropylidene derivative **2** in a quantitative yield (Scheme 1).[10] Phosphono sugar 2 was further purified by recrystallization from chloroform-ether. The structure of the single crystal 2 was elucidated by X-ray crystallographic analysis[11] (Fig. 1, Tables 1 and 2).



Scheme 1. Synthesis of 1,4-anhydro-4-deoxy-2,3-O-isopropylidene-4-((*R*)-methoxyphosphinyl)-L-ribitol (2). Reagents: i: H$^+$, acetone.

Table 1. Selected bond distances (Å)

P(0)-C(1)	1.796(3)	C(4)-P(0)	1.813(3)
C(1)-C(2)	1.522(4)	P(0)-O(3)	1.480(2)
C(2)-C(3)	1.559(4)	P(0)-O(4)	1.585(2)
C(3)-C(4)	1.544(4)	C(4)-C(5)	1.520(4)

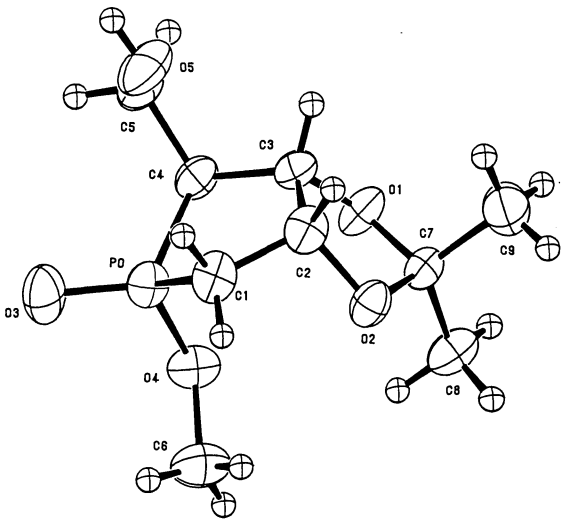


Fig. 1. Molecular structure of 2.

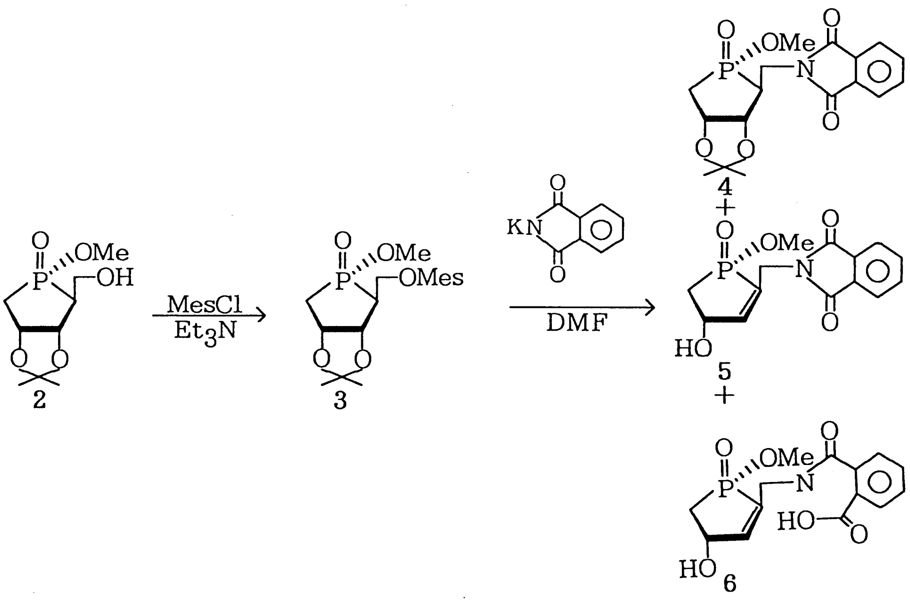
Table 2. Selected bond angles (°)

P(0)-C(1)-C(2)	104.6(2)	C(1)-C(2)-C(3)	111.8(2)
C(2)-C(3)-C(4)	111.6(2)	C(3)-C(4)-P(0)	104.1(2)
C(4)-P(0)-C(1)	96.6(1)	P(0)-C(4)-C(5)	113.4(2)
C(3)-C(4)-C(5)	119.3(3)	O(1)-C(3)-C(4)	110.2(2)
O(1)-C(3)-C(2)	104.3(2)	O(2)-C(2)-C(3)	103.6(2)
O(2)-C(2)-C(1)	108.9(3)	O(1)-C(7)-O(2)	104.2(2)
O(5)-C(5)-C(4)	107.3(3)		

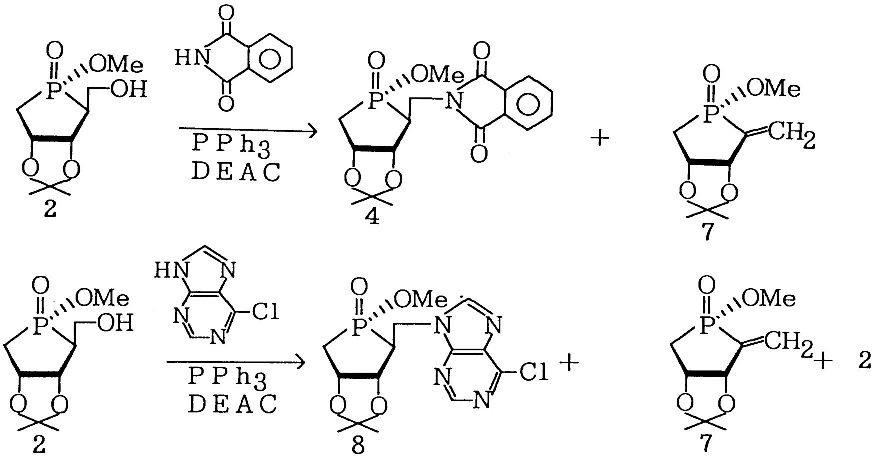
Reaction of compound 2 with methanesulfonyl chloride in CH_2Cl_2 in the presence of triethylamine at 0 ℃ for 1 d gave *O*-mesylated phosphono sugar derivative 3 in 69% yield. Successive reaction of compound 3 with potassium phthalimide in DMF at 80 ℃ for 8 h followed by separation by thin layer chromatography on silica gel gave phthalated compound 4 (24%), together with phthalated and dehydrated compound 5 (29%) and ring opened compound 6 (ca. 10%) (Scheme 2). The byproducts 5 and 6 may presumablely be prepared from product 4 by further reaction in basic solvent at high temperature for prolonged reaction time.

Synthesis of compound 4 was attempted by a separate method. Reaction of compound 2 with phthalimide under the condition of Mitsunobu reaction[12] (triphenylphosphine and diethyl azodicarboxylate in THF at 0 ℃

for 2 d) gave compound 4 in 65% yield and exocyclic olefinic compound 7 (trace) upon separation by thin layer chromatography on silica gel (Scheme 3).



Scheme 2. Preparation of phthalated phosphono sugar 4 by nucleophilic substitution reaction with potassium phthalimide.



Scheme 3. Preparation of compounds 4 and 8 by dehydration reaction of 2 with phthalimide and 6-chloropurine under Mitsunobu reaction.

For the preparation of the phosphono sugar nucleoside the same reaction mentioned above was carried out using 6-chloropurine. Reaction of compound 2 with 6-chloropurine under the condition of Mitsunobu reaction (triphenylphosphine and diethyl azodicarboxylate in THF at 0 ℃ for 1.5 d) gave a novel phosphono sugar nucleoside derivative 8 (28%), exocyclic olefinic compound 7 (21%), and the recorvered compound 2 (41%) upon separation by thin layer chromatography on silica gel (Scheme 3).

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9) Compounds **1**-**8** dealt with in this letter consist of the racemates, and the structural formulae represent one of enantiomers (*R*-form) prepared.

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11) Crystal data for **2**: $C_9H_{17}O_5P$, monoclinic, space group $P\,2_1/c$, a = 11.020(2), b = 5.919(2), c = 17.687(1) Å, β = 97.030(8)°, U = 1145.0(3) Å^3, Z = 4, D_c = 1.370 g·cm^{-1}, μ (M_o-K_α) = 2.32 cm^{-1}. The final cycle of full-matrix least squares refinement was based on 1682 observed reflections [$I > 3.00\sigma(I)$] and 204 variable parameters and converged with unweighted and weighted agreement factors of R = 0.044 (R_W = 0.052).

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